Looping the link between Gaucher and Parkinson’s disease

References


Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies
Mazzulli et al. (2011)
Cell 146(1): 37–52

Synucleinopathies are a subgroup of neurodegenerative disorders. The disorders are variable in their symptoms and expression, ranging from adult-onset Parkinson’s disease (PD) to Gaucher disease (GD), which presents in early childhood. However, while clinically distinct, they share a common pathologic lesion caused by deposits of α-synuclein (α-syn) aggregates in neurons and glia (1). A recent study by Mazzulli et al. (2) suggests a plausible biochemical link between two synucleinopathies – PD and GD – providing further understanding of the causes of neurodegeneration in these conditions and potential pathways for treatment targets.

The research premise Mazzulli and colleagues present is based on exploring the described clinical link between GD and Parkinsonism. GD is an autosomal recessively inherited disorder consisting of three subtypes, depending on symptom onset, progression and central nervous system (CNS) involvement. The disease is caused by a mutation in the glucosidase, beta, acid (GBA) gene, which is responsible for encoding glucocerebrosidase (GCase). GCase is a lysosomal enzyme that cleaves the β-glucosidic bond of its principal natural substrate, glucosylceramide (GlcCer). A deficiency GCase results in the accumulation of GlcCer in affected tissues including the liver, spleen and bone marrow.
Recognition of a higher incidence of PD in carriers of GBA mutations, as well as Parkinsonism findings in some patients with later onset GD, suggests a possible link between GlcCer metabolism and α-syn levels. Mazzulli et al. set out to explore the mechanism underlying this link further, ultimately theorizing a positive feedback loop between decreased GCase, increased α-syn and neurodegeneration (2).

Under normal circumstances, GCase (via the endoplasmic reticulum-Golgi pathway) activity in the lysosome degrades α-syn and prevents α-syn accumulation. However, in the presence of a GBA mutation, this pathway may become disrupted and this heterozygosity leads to the decreased expression of GCase. A positive feedback loop then occurs in which a deficiency in GCase leads to lysosomal accumulation of GlcCer in neurons. This accumulation in turn promotes the formation of insoluble neurotoxic α-syn amyloid fibrils. The increased levels of these toxic α-syn fibrils block intracellular trafficking and normal function of GCase in neural lysosomes. This leads to a further increase in GlcCer accumulation, propagating further formation of insoluble α-syn amyloid fibrils and so on (Fig. 2). Mazzulli et al. suggest that this loop will continue to self-propagate with age until α-syn reaches a toxic pathogenic level, and Parkinsonian disease symptoms present.

The authors present compelling evidence for an underlying biochemical mechanism linking GD and PD. The research also generates novel therapeutic targets, as disrupting the pathogenic feedback loop at any point in the cycle should both promote GCase activity and decrease α-syn accumulation. However, it is unclear whether the acute experiments and results presented will be relevant to a complex human disease that presents over many years (3). The challenge now is to replicate and build on these findings to further advance our understanding of both the rare and more common synucleinopathies. Nonetheless, this research does represent an important step forward in this devastating group of disorders, slowly paving the way for therapies of potential benefit across not just one but many conditions.

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